

Platelet thromboxane B₂ production in neonatal pulmonary hypertension

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SUMMARY Production of platelet thromboxane B₂, a stable metabolite of thromboxane A₂, was measured in seven newborn infants with pulmonary hypertension during the first day of life. Platelet thromboxane B₂ production was significantly lower than in 12 healthy controls but did not correlate with simultaneous blood gas values.

Persistent pulmonary hypertension of the newborn, characterised by pulmonary arterial vasoconstriction and right to left shunting at the level of the foramen ovale or ductus arteriosus, or both, is often associated with severe hypoxic disorders of the neonate.¹ The exact mechanisms leading to persistent pulmonary hypertension of the newborn are still largely unknown, although changes in prostanoid metabolism have been suggested.² Thromboxane A₂ is a potent proaggregatory and vasoconstrictory prostanoid produced and released by the platelets during aggregation.³ It is rapidly metabolised to its stable breakdown product, thromboxane B₂.³ To study synthesis of thromboxane A₂ in pulmonary hypertension production of platelet thromboxane B₂ during spontaneous clotting was measured in seven infants with persistent pulmonary hypertension of the newborn during the first day of life.

Patients and methods

Seven infants with persistent pulmonary hypertension of the newborn were studied with the approval of the local committee of ethics. The clinical data of these infants are presented in the Table. All infants needed ventilatory help and one patient (case 2) who had severe meconium aspiration syndrome subsequently died at the age of 4 days. The diagnosis of pulmonary arterial hypertension was based either on clinical and echocardiographic findings (cases 1 and 3–6) or on direct measurement of the pulmonary pressure (cases 2 and 7). An umbilical arterial catheter for monitoring of blood gas and fluid infusion was inserted in all infants. Twelve healthy control infants with comparable birth weights, gestational ages, and Apgar scores were similarly studied. The controls were selected

randomly and were studied over the same period as the patients. No mother in the study had taken any drugs known to interfere with prostanoid synthesis during the 10 days before delivery.

A blood sample (2.0 ml) from the umbilical arterial catheter in the study infants and from a peripheral vein in the controls was drawn into a dry test tube. Blood was first allowed to clot spontaneously for 60 minutes at 37°C and serum was then separated and measured for thromboxane B₂ radioimmunologically, as previously described.⁴ The results were expressed as nanograms of thromboxane B₂ per 10⁶ platelets and were analysed using the Mann-Whitney rank sum test.

Results

The median serum thromboxane B₂ concentration in our patients was 0.23 ng/10⁶ platelets (range 0.06–1.20 ng/10⁶ platelets), which was significantly (*p* < 0.02) lower compared with the healthy controls at the same age (0.95 ng/10⁶ platelets; range 0.61–1.65 ng/10⁶ platelets). There was, however, no correlation between the production of platelet thromboxane B₂ and the simultaneous blood gas values.

Table Clinical data on the seven newborn infants with persistent pulmonary hypertension

Case No	Birth weight (g)	Gestational age (weeks)	Apgar score		Clinical diagnosis
			At one minute	At five minutes	
1	4810	41	2	4	Meconium aspiration syndrome
2	3860	39	4	7	Meconium aspiration syndrome
3	4390	40	7	8	Meconium aspiration syndrome
4	2300	37	5	8	Meconium aspiration syndrome
5	2910	36	7	8	Respiratory distress syndrome
6	2200	36	9	9	Respiratory distress syndrome
7	3400	39	9	9	Down's syndrome, idiopathic pulmonary hypertension

Discussion

Persistent pulmonary hypertension in the newborn has a multiple aetiology and occurs in a variety of neonatal disorders. There is considerable evidence that thromboxane A₂ is involved in at least some forms of pulmonary hypertension.²⁻⁵ Infusion of live group B β haemolytic streptococcus, streptococcal toxin, or purified *Escherichia coli* endotoxin in animal models causes pulmonary hypertension, which is associated with high plasma thromboxane B₂ concentrations.⁵ It has also been suggested that pulmonary hypertension seen in perinatal aspiration syndrome is mediated by release of platelet thromboxane A₂ in the lungs.² Inhaled amniotic fluid may be absorbed by the lungs and cause local platelet aggregation. Thromboxane A₂ is then released from the platelets and causes pulmonary vasoconstriction.²

Our results suggest that production of platelet thromboxane A₂ is decreased in persistent pulmonary hypertension of the newborn. The lowest values were found in cases of severe meconium aspiration syndrome, but no correlations between the simultaneous blood gas values and production of platelet thromboxane B₂ were found. Although samples in the two groups were drawn from different sites, this should not influence the thromboxane B₂ results because they were expressed as nanograms per number of platelets. The high plasma thromboxane B₂ concentration in previous studies^{5,6} may originate either from the lungs or from hyper-reactive platelets, which release thromboxane B₂ excessively in vivo. If this in vivo stimulation of the release of thromboxane B₂ lasts long enough it may lead to exhaustion of the capacity of the platelets to

produce thromboxane B₂. The present in vitro data on reduced production of platelet thromboxane B₂ may support this hypothesis.

Vasoactive prostanoids and their inhibitors may be useful in the treatment of some forms of pulmonary hypertension. Selective inhibition of thromboxane A₂ formation is effective in some examples of experimental pulmonary hypertension.⁵ The biological antagonist of thromboxane A₂, prostacyclin, has been successfully used to reduce pulmonary hypertension.⁶ The response to this treatment with dilator could be enhanced if the platelet formation of the vasoconstrictive thromboxane A₂ is already diminished, as in the present cases.

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Noonan's syndrome and neurofibromatosis

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SUMMARY A child with Noonan syndrome and multiple café au lait spots, compatible in size and number with von Recklinghausen's neurofibromatosis, is presented. These features may represent a distinct genetic entity rather than the coincidence of two diseases.

Noonan's syndrome share several similar clinical findings, such as short stature, mental retardation, pubertal changes, kyphoscoliosis, and right sided congenital heart disease.^{1,2} Multiple café au lait spots are regarded as pathognomonic of von Recklinghausen's neurofibromatosis³ and have not been reported with Noonan's syndrome.² A few children have been reported recently with typical features of Noonan's syndrome and multiple café au lait spots and were diagnosed as neurofibromatosis-Noonan's

Von Recklinghausen's neurofibromatosis and